

New determinants for causal neural mechanism of dry mouth in Parkinson's disease induced by destruction of superior salivatory nucleus, facial nerve, and submandibular gland circuitry: an experimental study

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ABSTRACT

Aim: Dry mouth has been considered a clinical finding of Parkinson's disease (PD), but we think otherwise. We studied if the olfactory bulbectomy (OBX) might rely on the superior salivatory nucleus (SSN), submandibular ganglia (SMGn), and submandibular glands (SLGI) circuitry disruption induced submandibular gland degeneration related dry mouth in rats.

Material and Method: This study was carried out on twenty-six male rats. Five (GI-n=5), six (GII, n=6), and sixteen (GIII, n=15) of them were used as control, SHAM, and OBX groups, respectively, and followed eight weeks. PD-related clinical examinations were done before and after the experiment (1/day), and animals were decapitated. The olfactory bulb volumes (mm^3), degenerated neuron densities of SSN/SMG (n/mm^3) and SMGI follicles volumes were detected serologically. Olfactory bulb volume values and degenerated neuron density values of SSN/SMGn/SMGI follicles volumes were compared statistically.

Results: OBX-applied animals showed anosmia, tremors, rigidity, and memory loss. The mean olfactory bulb volumes (mm^3), degenerated neuron density of SSN (n/mm^3), SMGn (n/mm^3), and follicles volumes of SMGI (cubic micrometer/ mm^3) were measured in the order written as; (4.27 ± 0.21), (4 ± 1), (5 ± 2), (81.23 ± 13.34).106 in GI; (3.67 ± 0.33), (14 ± 3), (17 ± 4), (72.45 ± 11.78).106 in GII and (2.91 ± 0.14), (23 ± 5), (29 ± 8), (57.19 ± 11.93).106 in Group III. The mean P values between olfactory bulb volumes, degenerated neuron densities of SSN and SMGn, and salivary follicles volumes were: $p < 0.005$ in GI/GII; $p < 0.0005$ in GII/GIII; $p < 0.0001$ in GI/GIII.

Conclusion: OBX-related olfactory network designalisation may be responsible for SSN/SMGn circuitry degeneration-induced SMGI atrophy-based dry mouth. The OBX-related dry mouth should be considered a causative factor for Parkinson's disease, not a result.

Keywords: Olfactory bulbectomy, salivatory nucleus, submandibular ganglion, facial nerve, salivary gland

INTRODUCTION

Anosmia and ageusia are the most common and frequent nonmotor features of Parkinson's disease (PD) (1). Olfactory involvement usually occurs together with parasympathetic dysautonomia (2). Psychiatric disorders and cognitive problems are also common manifestations (3). The olfactory impulses augment appetite, salivation, and food intake (4). Taste and smell loss decreases salivary secretions (5). The saliva is required for swallowing and digestion. Pavlov reported that classic conditioning could also secrete saliva (6). There is an important relationship between smell, taste, and salivary secretion. Smell disorders cause decreased salivary secretions (7). The odor augments appetite, salivation, and food intake (4). Taste and smell loss decrease in

parotid salivary functions (5). The facial nerve modulates parasympathetic innervation of the salivary, lacrimal, and paranasal-oral mucosal glands via postganglionic parasympathetic fibers of the pterygopalatine ganglion (8). Dry mouth, difficulty in slowing, and digestive disorders are troublesome components of PD. Because PD is accompanied by amyloid degeneration of the salivary secretion starting facial, glossopharyngeal, and vagal salivatory nuclei, sympathetic ganglia, and myenteric plexus (8). Facial nerve lesions lead to decreased salivary secretion (9). It has been reported that damage to the olfactory pathways causes the same neuropathological changes in neural nuclei and circuits that are frequent PD (10). If so, dry mouth caused by superior salivary nucleus-

facial nerve-submandibular gland circuitry disruption induced by olfactory signal loss should be considered the cause of Parkinson's disease, not as a causative agent for Parkinson's disease.

MATERIAL AND METHOD

The study was carried out with the permission of permission of Atatürk University, Faculty of Medicine, Ethics Committee for Animal Experiments (Date: 09.11.2022, Decision No: E-42190979-000-2200225459). All procedures were carried out under ethical rules and principles.

26 Wistar Albino male rats were included in this study. The test subjects were placed in single stainless steel cages at 21°C and cycles of light and dark with appropriate humidity. A standard feeding was given to test subjects for nutrition.

The subjects were divided into three random groups. For pain control balanced, injectable anesthetics were preferred. Isoflurane was applied by a face mask, 0.2 mL/kg of the combined drugs (Ketamine HCL, 150 mg/1.5 mL; Xylazine HCL, 30 mg/1.5 mL; and distilled water, 1 mL) was administered before the surgical procedures. The study groups were; the control group (Group I, n=5), the SHAM group, and (Group II, n=5). Burr holes were made, and olfactory bulbectomy (OBX) was not applied, and the study group, in which bilaterally OBX was done via a micro clamp (Group III, n=16), and all groups were observed for ten weeks. During the ten weeks, all subjects were observed without any medical treatment. They were seen for noticing their vital findings with ten minutes periods two times a day during the experiment. The test subjects' olfactory functions, appetite status, and weight were recorded. After ten weeks of follow-up, all subjects were decapitated under general anesthesia. The total brain structures of all test subjects were stored in 10% formalin solutions for seven days. After cleaning procedures, all tissue specimens underwent histologic evaluation.

The volumes of olfactory bulbs were measured and recorded macro anatomically. Both olfactory bulbs, brainstem, superior salivatory nucleus (SSN), and SLGI sections were stained with GFAP and hematoxylin-eosin. Olfactory bulbs and superior salivary nuclei sections were stereologically analyzed. With olfactory bulb volume values, degenerated neuron densities of the superior salivary nucleus and submandibular ganglion and follicle volumes of the SLGI were compared.

Histopathological Procedures

The olfactory bulbs were sliced in 5 µm thickness at each 30 µm length. Every 28th and 29th, section were sampled to calculate the volume of olfactory bulbs.

The fractioner method studies the total number of olfactory bulb glomerulus. Specimen slices were stained with hematoxylin-eosin (H&E) and GFAP methods and examined under a light microscope. To detect the olfactory nerve lesion, portions were taken parallelly to the long axis of the nerves. The same procedures were performed for the SSN to reveal histology.

Stereological Analysis

Stereological methods have a significant role in the estimation of particle density. Stereological methods determine the number of a particle per unit volume by the integral method. Suppose the point taken as a reference in one of two consecutive parallel sections taken from the tissue to be examined at intervals smaller than the diameter of the particle to be estimated is not present. In that case, it is taken as a disector pair and included in the count.

In our study, sections were cut with measurements corresponding to values below the nucleus diameter of the neuron cells to be examined. The physical dissecting method was used. Therefore, 20 sections of 3 microns passing through the plane of the superior salivator nucleus; 20 sections of 5 microns passing through the plane of the ganglion were taken from the SLGI. The physical dissection method was also performed to determine degenerated neurons in the superior salivary nucleus. In Kolmogorov-Smirnov and Shapiro-Wilk tests, there was no normal distribution in all groups ($p < 0.05$). The Mann-Whitney-U test was applied to the separately compared groups for independent samples compared in pairs and then analyzed with the Kruskal-Wallis test. For the p-value used for multiple comparisons by dividing 0.05 by six with Bonferroni regulation, a value of $p \leq 0.0098$ was considered significant. Statistically, the p-value was considered significant at the 0.05 level. (Confidence interval 95%). Since the olfactory bulbs resemble an ellipsoid, the volume values were also estimated by the volume formula of the ellipsoid (10). Follicle volumes of the salivary glands were measured with the method Aydin N et al. used to measure the thyroid gland follicle volumes. Data were analyzed using the method (SPSS® for Windows v. 12.0, Chicago, USA). Data analysis consisted of the Kruskal-Wallis and Mann-Whitney U tests. Differences were considered significant at $p < 0.05$.

RESULTS

Anosmia, finger tremors during food selection, rigidity, and loss of memory were seen in OBX-applied subjects. To evaluate the finger tremor sign, which is the typical finding of PD, the subjects were subjected to tests to determine tight-handedness. Tremors more than six times per minute were found to be significant. Histopathological

evaluation of the specimens was demonstrated in **Figures 1-5**. OOBX-applied animals showed anosmia, tremors, rigidity, and memory loss. The mean olfactory bulb volumes (mm^3), degenerated neuron density of SSN (n/mm^3), SMGn (n/mm^3), and follicles volumes of SMGI (cubic micrometer/ mm^3) were measured in the order written as; (4.27 ± 0.21) , (4 ± 1) , (5 ± 2) , $(81.23 \pm 13.34) \cdot 106$ in GI; (3.67 ± 0.33) , (14 ± 3) , (17 ± 4) , $(72.45 \pm 11.78) \cdot 106$ in GII and (2.91 ± 0.14) , (23 ± 5) , (29 ± 8) , $(57.19 \pm 11.93) \cdot 106$ in Group III. The mean P values between olfactory bulb volumes, degenerated neuron densities of SSN and SMGn, and salivary follicles volumes were: $p < 0.005$ in GI/GII; $p < 0.0005$ in GII/GIII; $p < 0.0001$ in GI/GIII.

In macroscopic evaluation decrease in olfactory bulb volume, obstruction of the ethmoid foramen, thickening and adhesions in the dura and arachnoid membranes inflammatory changes in the subfrontal area was seen. Histopathologically degeneration in glomerules of olfactory bulbs, decrease in glial cell density and interneuronal connections, and inflammatory changes in olfactory bulbs were evaluated. Inflammation, adhesions, thickening in dural structures, and ischemic pathologies were observed. In the analysis of salivary nuclei, neuronal degeneration such as cytoplasmic and nuclear condensation, pericytoplasmic halo formation, dendritic fragmentation, cellular angulation, and neuronal loss existed. In the control group, minimal, sham mild, study severe changes were observed. Specific findings of the histopathological evaluation were demonstrated in **Figures 1-5**.

In the microscopic analysis of sublingual glands, SSN and sublingual ganglion (SLGn) degenerated neurons were rarely observed in the control group because of postmortal degeneration due to technical reasons. Still, mild degeneration was observed in the SHAM group, and severe degeneration was observed in the study group.

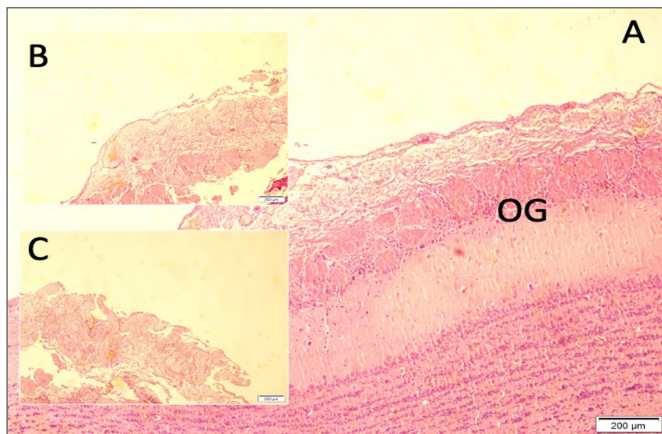


Figure 1. Vertical sections of the olfactory bulb in a normal subject shows the histological structures of the olfactory nerve and the olfactory glomeruli that we examined. A subject from the SHAM group has a partially deformed olfactory bulb (in figure B), and a subject from the study group has a significantly deformed olfactory bulb in figure C (Light Microscope, H&E, 4X magnification/A, B, C).

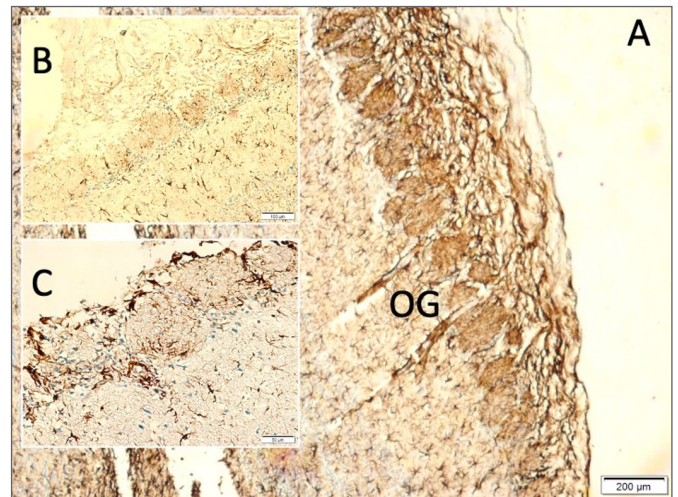


Figure 2. By the immunohistochemical method, Vertical sections of the olfactory bulb in a normal subject show the histological structures of the olfactory nerve and the olfactory glomeruli we examined (in figure-A. A subject from the SHAM group has a partially deformed olfactory bulb in figure B, and a subject from the study group has a significantly deformed olfactory bulb in figure C (LM, GFAP, x4/A, B, C).

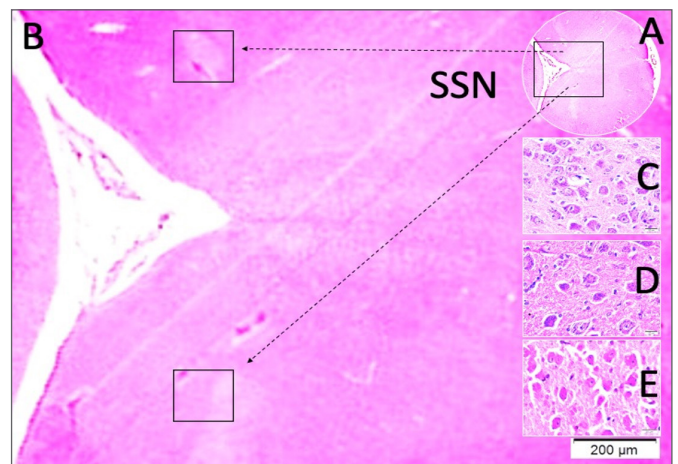


Figure-3. localization of the nucleus salivary superior (A, B) and normal nucleus neurons (C), moderately degenerated neurons of the SHAM group (D), and highly deformed neurons of the study group are observed in a rat (LM, HE, x4/A; x20/C-E).

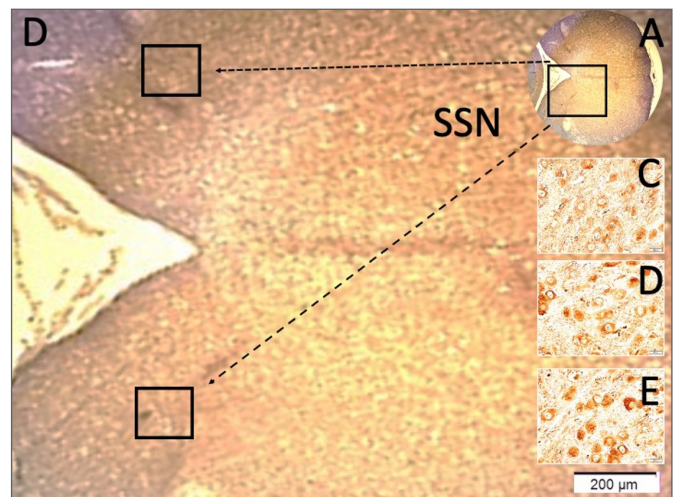


Figure-4. localization of the nucleus salivary superior (A, B) and normal nucleus neurons (C), mildly degenerated neurons of the SHAM group (D), and highly deformed neurons of the study group are observed in a rat (LM, GFAP, x4/A; x20/C-E).

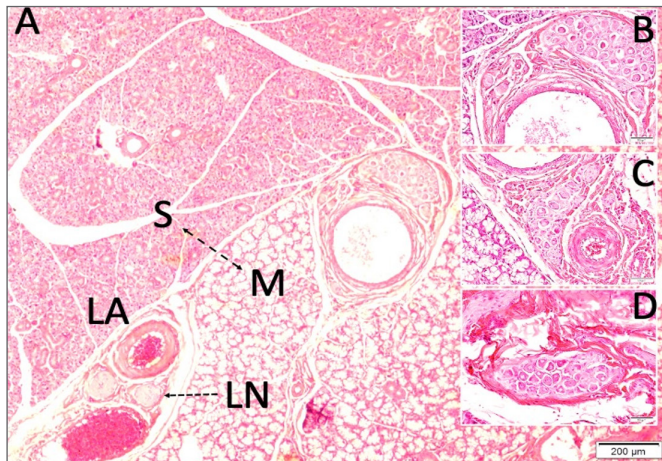


Figure-5. In a normal subject, the serous (S) and mucous (M) parts of the submandibular gland, lingual artery branch (LA), and lingual nerves branch (LNb) are observed. Again, submandibular ganglion in a normal subject; moderately degenerated neurons included SLG in group 2; and high degeneration in neurons included submandibular ganglion belonging to group 3 (LM, H&E, x4/A: x20/BCD).

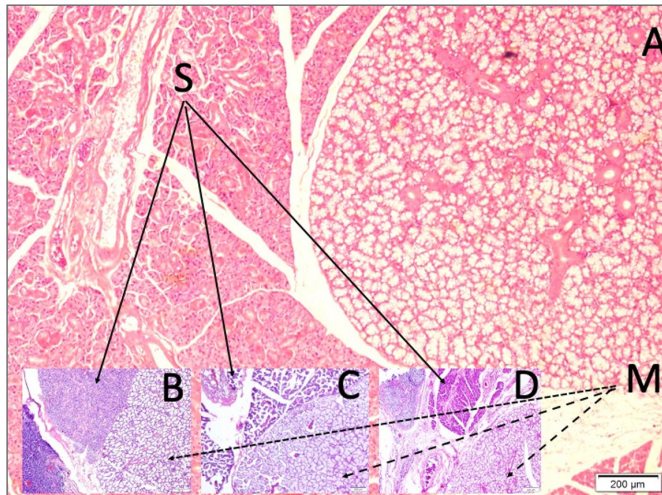


Figure-6. In a normal subject, the serous-mucous parts of a submandibular gland (A-B); moderately degenerated epithelial cells included salivary gland in group 1 (C); and severely high degeneration in epithelial cells included salivary gland submandibular ganglion belonging to group 3 (D)(LM, H&E, x4/A: x20/B, C, D, Serous S, Mucous M)

DISCUSSION

An important anatomical, physiological, and even psychological interaction exists between the senses of smell, taste, and salivary secretion. Smell disorders cause a significant loss in eating habits and quality of life. Changes in odor perception also negatively affect food taste. Olfactory dysfunction dangerously affects taste sensitivity and saliva secretion (7). The odor augments appetite, salivation, and food intake (4). Taste and smell loss decrease parotid salivary functions (5). The secretion of saliva is an important physiological function for swallowing and digestion. Pavlov reported a century ago that saliva in dogs could also be secreted by classical ring-tone conditioning (6). Odor stimuli play an important role in the perception of ingested food

flavor. Food-related odors have been shown to induce appetite, salivation, gastric acid, and insulin secretion (11). Olfaction stimulates salivary secretions (12). Olfactory signals start salivary reflexes (13). Olfactory impairment and depression can be seen in the onset of PD motor manifestations (14). Anosmia and ageusia are common nonmotor features of PD (15, 16). Olfactory involvement leads to parasympathetic dysautonomia (2). The amygdala-hippocampal complex is functionally implicated in conditioned olfaction and taste aversion in learning memory and autonomic functions required for food selection, eating, and metabolism (17).

The SSN is the primary parasympathetic center of the submandibular and sublingual salivary glands. Their neurons receive excitatory impulses from facial and glossopharyngeal nerves; inhibitory impulses come from cervical sympathetic (18). The SSN is a part of the reticular formation and is placed between the trigeminal nerve's facial nucleus and spinal nucleus. The salivatory nucleus extends from a level at the facial nucleus's caudal border through the facial nerve's genu (19). The SSN includes neurons that supply the intra-glandular submandibular ganglion. The SSN cells are typical preganglionic autonomic neurons (20). Preganglionic neurons of the SSN receive excitatory inputs from the solitary tract and the central nucleus of the amygdala (21, 22). The SSN innervates the submaxillary and sublingual salivary glands by preganglionic fibers (23). The SSN sends parasympathetic axons to salivary glands (24). The parasympathetic neurons of the SSN controls the parotid and von Ebner salivary glands (25). SSN stimulation causes salivation from sublingual-submandibular glands (26). Stimulation of the chords-lingual nerve evoked saliva secretion from oral glands. Sympathetic nerve stimulation decreased saliva secretion (27).

Facial Nerve - Superior Salivatory Nucleus Relations

The facial nerve includes the motor, sensory and parasympathetic fibers (28). The general visceral motor part gives autonomic parasympathetic innervation to the lacrimal, salivary, and paranasal-oral mucosal glands (29).

When afferent signals from smell, taste, and chewing reach the central nervous system, they initiate salivation from the salivary glands. Fluid salivary secretion generally depends on parasympathetic cholinergic signals, while sympathetic nerves, neuro peptides, and noradrenaline signals salivary secretion. Since the salivary glands have regenerative abilities, The autonomic nerves that innervate them have a role in regeneration, gland development, also maintaining their long-term normal functions. We come across experimental findings that the destruction of the olfactory pathways also negatively affects the sympathetic nervous system.

In previous studies of Aydin et al. SLGI lesions and atrophy was studied in 10 weeks time to establish substantia nigra degeneration. In this study we have studied for 8 weeks time. In this study, we made a more specific examination by also analyzing the superior salivatory nuclei of the facial nerve to investigate the more rational cause of dry mouth. The olfactory bulb sends signals to the superior salivatory nucleus, which is related to the facial nerve, via the olfactory pathways, which sends parasympathetic impulses to the sublingual and submandibular glands, which we focused on in our study, unlike the previous ones. Interruption of the olfactory pathways causes denervation injury in the SSN. This injury also causes denervation injury in sublingual and submandibular glands. Both injuries disrupt secretion production in salivator glands and reveal atrophy, which we analyzed volumetrically, different from other studies.

Olfactory Bulb Lesion Induced Clinico-Histopathological Problems Mimic Parkinson's Disease

Odor stimuli play a major role in the perception of food flavor, appetite, salivation, and release of enzyme and hormone secretion to the metabolism of foods (11). Olfactory bulb lesions lead to substantia nigra degeneration, mammary gland insults, Peyer's patches hyperplasia induced by infections, hypothyroidism, neuropsychiatric disorders, sexual problems, Hirschprung-like disease, and spermatogenesis disorders (10, 30-35). The findings summarized under this title are generally observed in PD. However, the events that caused these findings were recorded as symptoms of PD. According to us, the correct information is that these events started PD. Since the regeneration capacity of olfactory nerves and glands is present, we also observed that the secretory activities returned in some subjects.

Brain Stimulation and Olfaction Relations in Parkinson's Disease

Deep brain stimulation is an effective treatment method to improve motor and olfactory function and odor identification (36, 37). Deep brain stimulation of the subthalamic nucleus may also improve olfaction and constipation (38). Subthalamic and pallidal deep brain stimulation improves the quality of life, motor, and nonmotor (39). Reversible improvement occurs in olfactory dysfunction after subthalamic nucleus stimulation (40). Chronic high-frequency stimulation of the subthalamic nucleus induces neurogenesis in the hippocampus and olfactory bulb and ameliorates mood disorders and olfaction deficits (41). Neuroregeneration occurring in olfactory bulbs can improve the course of alarming findings.

Deep Brain Stimulation and Salivation

Deep brain stimulation ameliorates gastrointestinal dysfunctions (42). Subthalamic nucleus deep brain stimulation is an important option for treating eating, sweating, absorption, metabolism, and excretion disorders (43). Deep brain stimulation also modulates oropharyngeal swallowing process arising from olfactory disorders. We continue to work on how noninvasive olfactory stimulation can be more beneficial than a breakthrough.

Limitation: This study only includes experimental results.

CONCLUSION

OBX-related olfactory network designalisation may be responsible for SSN degeneration, and related dry mouth is the first symptom of PD. Facial nerve pathologies may cause dry mouth. If so, olfactory signal loss induced superior salivatory nucleus-facial nerve-salivary gland circuitry disruption may lead to dry mouth and ageusia, which has not been mentioned in the literature so far. Energy failure due to neurodegeneration in the SSN may be responsible for dry mouth in Parkinson's disease.

Future Insights: This method, which has been examined in the pathology of Parkinson's, may also open up horizons for these mechanisms in treatment. We can predict from our studies that noninvasive olfactory nerve, facial nerve, glossopharyngeal nerve, and trigeminal nerve stimulations can be used in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of permission of Atatürk University, Faculty of Medicine, Ethics Committee for Animal Experiments (Date: 09.11.2022, Decision No: E-42190979-000-2200225459).

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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